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Mortality Following Nonfatal Opioid and Sedative/Hypnotic Drug Overdose

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Abstract

Introduction: Opioid and sedative/hypnotic drug overdoses are major causes of morbidity in the U.S. This study compares 12-month incidence of fatal unintentional drug overdose, suicide, and other mortality among emergency department patients presenting with nonfatal opioid or sedative/hypnotic overdose.

Methods: This is a retrospective cohort study using statewide, longitudinally linked emergency department patient record and mortality data from California. Participants comprised all residents presenting to a licensed emergency department at least once in 2009–2011 with nonfatal unintentional opioid overdose, sedative/hypnotic overdose, or neither (a 5% random sample). Participants were followed for 1 year after index emergency department presentation to assess death from unintentional overdose, suicide, or other causes, ascertained using ICD-10 codes. Absolute death rates per 100,000 person years and standardized mortality ratios relative to the general population were calculated. Data were analyzed February–August 2019.

Results: Following the index emergency department visit, unintentional overdose death rates per 100,000 person years were 1,863 following opioid overdose, 342 following sedative/hypnotic overdose, and 31 for reference patients without an index overdose (respective standardized mortality ratios of 106.1, 95% CI=95.2, 116.9; 24.5, 95% CI=21.3, 27.6; and 2.6, 95% CI=2.2, 3.0). Suicide mortality rates per 100,000 were 319, 174, and 32 following opioid overdose, sedative/hypnotic overdose, and reference visits, respectively. Natural causes mortality rates per 100,000 were 8,058 (opioid overdose patients), 17,301 (sedative/hypnotic overdose patients), and 3,097 (reference patients).

Conclusions: Emergency department patients with nonfatal opioid or sedative/hypnotic drug overdose have exceptionally high risks of death from unintentional overdose, suicide, and other causes. Emergency department–based interventions offer potential for reducing these patients' overdose and other mortality risks.

INTRODUCTION

Drug-related morbidity and mortality in the U.S. represent serious ongoing public health challenges. Drug overdose mortality rates increased 225% between 1999 and 2015,[1] alongside a concomitant rise in nonfatal drug overdoses.[2–5] Prescription opioids and heroin have been responsible for the majority of drug overdose mortality during this epidemic[1]: In 2017, there were 32,511 deaths from prescription opioids or heroin, and 28,466 deaths from synthetic opioids (e.g., fentanyl).[6] Prescription sedative/hypnotic drugs such as benzodiazepines, however, are involved in a large[7] and increasing[8] proportion of nonfatal drug overdoses.

Although several reports have described trends and patterns of visits to emergency departments (EDs) involving opioid- and sedative/hypnotic-related harm,[5,9–13] less is known about the risks of mortality following nonfatal overdoses. A few studies have reported high all-cause and cause-specific mortality rates among opioid overdose patients from Massachusetts[14–16] and Medicaid programs[17] but broader examinations of mortality among overdose patients in large general populations are lacking. Such information could inform clinical and public health prevention efforts aimed at reducing these individuals' mortality risks.[18–20]

The present study compared 12-month prospective rates of all-cause and cause-specific mortality among residents of California with ED visits for either opioid or sedative/hypnotic drug overdose, as well as among a reference sample of other ED patients. The ED serves as a key clinical entry point for patients experiencing unintentional drug overdose, and thus offers an important setting for identifying patients at elevated risk for fatal unintentional overdose and other mortality outcomes.[5,18,21,22]

Opioid and sedative/hypnotic misuse may be differentially associated with mortality risk. Prescription opioids, as compared with sedative/hypnotic drugs, have a narrower therapeutic index and greater interpatient variability in response,[23] potentially leading to a greater hazard of fatal overdose.[24–26] As compared with the general population, all-cause mortality appears to be elevated following nonfatal opioid overdose[16,17,27] and among patients who are prescribed sedative/hypnotic drugs.[28–31] Yet, the comparative all-cause and cause-specific risks of mortality following opioid vs. sedative/hypnotic overdose remain unknown. In addition to risks of drug overdose deaths, risk of suicide deaths may be of particular interest, given the uncertainty in determining intent among overdose decedents[32] and the implications for prevention.[33] Use of both classes of drugs has been linked to suicidal behavior,[19,34] but whether opioid versus sedative/hypnotic overdose is more strongly associated with suicide differs is unclear.[35–37]

The authors hypothesized that rates of all-cause and unintentional drug overdose fatality would be higher among opioid overdose patients compared to sedative/hypnotic overdose patients, and that both rates would be higher than among ED patients without either opioid or sedative/hypnotic overdoses. This study also tested whether suicide rates differed between sedative/hypnotic overdose patients relative to opioid overdose patients. Lastly, because sedatives can potentiate opioid-related respiratory suppression,[38,39] this study tested whether opioid overdose patients whose index overdoses also involved sedative/hypnotics experienced higher rates of drug overdose death.

METHODS

Discharge data were obtained from the California Office of Statewide Health Planning and Development on all visits in 2009–2011 to all California-licensed EDs by individuals aged 10 years with a California residential ZIP code. This office also provided information on all individuals in this ED cohort to the California Department of Public Health Vital Records, which assessed vital status in California death records and provided information on date and cause of death for all matching decedents who died in 2009–2012 (excluding those who died out of state, <1% of the total). All data obtained and used by the study team were de-identified. This study was approved by the IRBs of the California Health and Human Services Agency and the University of California, Merced. Data were analyzed February–August 2019.

Study Sample

This cohort was partitioned into three non-overlapping groups: (1) all patients with opioid overdose, defined as those with at least one ED visit during the 2009–2011 study period that included an ICD-9-CM code in any diagnostic position corresponding to unintentional poisoning by heroin, methadone, or related opiates and narcotics; (2) all patients with sedative/hypnotic drug overdose, defined as those with at least one ED visit during the period that included an ICD-9-CM code corresponding to unintentional poisoning by barbiturate, benzodiazepine, or other sedative/hypnotic drug, but none with an opioid overdose visit during the period; and (3) a 5% random sample of all other patients (hereafter termed "reference patients"). The groups were defined hierarchically, with the presence of an opioid overdose diagnosis considered first, and presence of a sedative/hypnotic overdose diagnosis considered second. Examined separately were the subgroup of opioid overdose patients with a comorbid diagnosis of sedative/hypnotic drug poisoning at index visit. The ICD-9-CM codes used to define each patient group are shown in Appendix Table 1. Qualifying drug (opioid or sedative/hypnotic) overdose visits could not include an ICD-9-CM code corresponding to deliberate self-harm (E950-E958). Since 1990, California has mandated 100% reporting of external cause-of-injury codes (E-codes), which describe the cause and intent of an injury in a single supplementary code.[40]

The analyses were limited to index visits, defined as follows. For drug overdose patients, their first qualifying ED visit during the study period was defined as their index visit. For reference patients, their first ED visit during the study period was defined as their index visit. For visits resulting in patient discharge or transfer to another facility, the index date

was the date of ED presentation. For visits that resulted in a same-hospital admission, the index date was the date of discharge from the associated hospitalization.[41] Patients whose index visit resulted in death were excluded from follow-up analyses.

For calculation of standardized mortality ratios (SMRs), data on death by manner for California overall in 2009–2012 were obtained from the Center for Disease Control's WONDER system.[42]

Measures

The primary outcomes were death within 1 year of the index date by unintentional drug overdose and by suicide. Suicide was examined both overall and disaggregated into drug overdose versus non-overdose suicides. Secondary outcomes included other manners of death, classified into non-overlapping categories: unintentional injuries not due to overdose, homicide, injury of undetermined intent, and deaths from natural causes. Rates of all-cause and all external cause (unintentional, suicide, homicide, and undetermined-intent injury) mortality were also calculated. The authors defined manners and causes of death based on ICD-10 codes (Appendix Table 2), where cause of death refers to the mechanism of the specific injury or disease that led to death and manner of death refers to the determination of how the injury or disease led to death.

Patient demographic characteristics were examined for descriptive purposes and to calculate SMRs. These characteristics included sex (male, female), age group (10–24, 25–44, 45–64, and 65 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/ Pacific Islander, other), and insurance status (private, Medicaid, Medicare, self-pay/other).

Statistical Analysis

Crude mortality rates per 100,000 person years of follow-up were calculated for all manners of death in the year after the index date, for each patient group respectively. Individuals who did not link to California mortality records from 365 days after the index date were presumed alive for this period. Decedents were treated as censored on their death date.

Annualized SMRs, defined as the ratio of the observed numbers of deaths in the ED cohorts to expected deaths, were calculated next. The numbers of expected deaths in California for 2009–2012 were calculated using the WONDER mortality database, standardized to the distribution of sex, age category, and race/ethnicity category of the respective ED groups.

Mortality rates in the opioid overdose and sedative/hypnotic overdose patient groups were compared with those in the reference patient group using Cox proportional hazards regression, adjusting for patient, age, sex, race/ethnicity, and payer at index visit. Given the large number of comparisons, the Bonferroni correction was applied and results were considered statistically significant if $p<0.0167$. Cox regression, adjusting for the same covariates, was also used to compare mortality rates in the subgroup of opioid overdose patients with a comorbid diagnosis of sedative/hypnotic drug poisoning to those in the subgroup without comorbid sedative/hypnotic poisoning. Lastly, within each patient group, log-rank tests were used to test for potential sex differences in unintentional overdose and suicide mortality.[17,43]

Statistical analyses were conducted using Stata, version 14.0.

RESULTS

A total of 21,465 opioid overdose patients, 77,358 sedative/hypnotic overdose patients, and 503,362 reference patients (representing a 5% random sample) had index ED visits. Patients with fatal index events (n=385, n=1,967, and n=3,146, respectively) were excluded from follow-up analyses. Sociodemographic characteristics of the patient groups varied. In general, sedative/hypnotic overdose patients were older and more frequently male and of non-Hispanic white race/ethnicity (Table 1).

The all-cause mortality rate among patients whose index visit involved non-fatal opioid overdose was 10,620 per 100,000 in the subsequent year, substantially higher than the demographically matched California population (3,236 per 100,000; SMR=9.9, 95% CI=9.4, 10.3) (Table 2). Among patients whose index visit involved non-fatal sedative/hypnotic drug overdose, the all-cause mortality rate was even higher (18,080 per 100,000), and was also significantly higher than the matched general population (SMR=8.6, 95% CI=8.5, 8.8). ED patients without opioid or sedative/hypnotic overdose visits had an all-cause mortality rate that was 3.1 times higher than that of the demographically matched general population.

Opioid overdose patients died from unintentional overdoses at a rate over 100 times higher than that of the demographically matched population (rate, 1,863 per 100,000 years; SMR=106.1, 95% CI=95.2, 116.9). Overdoses were responsible for a vast majority (88%) of all unintentional deaths in this patient group; 38.3% (n=141) of these deaths were due to opioid or other narcotic drugs. The suicide rate of opioid overdose patients (319 per 100,000; SMR=18.1, 95% CI=13.6, 22.6) was also elevated, particularly for overdose suicides (SMR=43.0, 95% CI=27.4, 58.7), 17.2% (n=5) of which implicated opioid or narcotic drugs. Homicide, undetermined-intent, and natural cause mortality rates were also significantly elevated relative to the demographically matched population. Deaths from natural causes made up 76% of all deaths in this group; the leading natural-death causes were circulatory system disease (26.9% of natural cause deaths), cancer (29.9%), and respiratory system diseases (15.3%) (data not shown in tables).

Unintentional overdose mortality rate among sedative/hypnotic overdose patients occurred at a rate nearly 25 times that of the general population (rate, 342 per 100,000; SMR=24.5, 95% CI=21.3, 27.6). Overdoses accounted for 60% of unintentional deaths in this patient group. The suicide rate of sedative/hypnotic overdose patients (174 per 100,000) was nine times higher than that of the general population (SMR=9.2, 95% CI=7.6, 10.9). Opioids or narcotics were implicated in 27.2% of unintentional overdose deaths and 8.6% of overdose suicides in this group. Homicide and undetermined-intent injury mortality rates were elevated relative to the general population. Deaths from natural causes accounted for 96% of all deaths in the sedative/hypnotic overdose patient group; leading causes were circulatory system disease (36.5%), cancer (21.7%), and diseases of the endocrine or metabolic systems (9.7%) (data not shown in tables).

Nearly 20% (*n*=4,186) of opioid overdose patients had a comorbid diagnosis of sedative/ hypnotic poisoning at index visit (Table 3). In covariate-adjusted Cox models, mortality in this subgroup, when compared with the subgroup without comorbid sedative/hypnotic poisoning, was significantly higher for unintentional injuries (hazard ratio=1.36, 95% CI=1.09, 1.70) and for all external injuries combined (hazard ratio=1.34, 95% CI=1.10, 1.65), but lower from natural causes.

The unintentional overdose injury mortality rate among reference patients was 31 per 100,000 (SMR=2.6, 95% CI=2.2, 3.0); these overdose fatalities made up just one third of their unintentional injury deaths (Table 2). Reference patients' suicide rate was 2.2-fold higher than the general population. Most deaths in this group (96%) were from natural causes, largely from either circulatory system disease (33%) or cancer (32%). In covariate-adjusted Cox regression models using reference patients as the comparison group, opioid overdose patients and sedative/hypnotic overdose patients had significantly higher mortality rates for each manner of death, with the sole exception of homicide among sedative/hypnotic overdose patients (Appendix Table 3). The magnitude of these hazard ratios was approximately half that of the SMRs calculated using the general California population.

Male patients were at greater risk than female patients for unintentional drug overdose death in the opioid overdose and reference patient groups (log-rank tests *p*<0.001), but female patients were at slightly greater risk in the sedative/hypnotic overdose group (log-rank test, *p*=0.03) (Figure 1). Risk of suicide was greater among male than female patients in the reference group (*p*<0.001), but not significantly so in either of the drug overdose groups (both *p*=0.10) (Appendix Figure 1).

DISCUSSION

This is the first population-based study from the U.S. to compare drug overdose, suicide, and other mortality rates following nonfatal opioid and sedative/hypnotic overdose presentations to the emergency department. The rate of unintentional drug overdose deaths among patients with a nonfatal opioid overdose was 100-fold higher than that of the demographically matched general population, and their rate of suicide was 18-fold higher. Unintentional overdose and suicide mortality rates among sedative/hypnotic overdose patients were 24- and 9-fold higher, respectively, relative to the general population. The magnitudes of increased risk were approximately half as large when using the reference patient group as the comparison. These findings provide robust support for the widespread implementation of ED-based interventions designed to reduce future overdose risk, not only among opioid overdose ED patients but also among ED patients presenting after overdose from sedative/ hypnotic drugs like benzodiazepines. Several interventions that did not exist during the study period have subsequently demonstrated promise for opioid overdose patients (including ED-initiated buprenorphine treatment, addiction counseling, and referral to outpatient care[15,44–46]) but remain infrequently used.[47–49]

The 12-month rate of unintentional overdose death following nonfatal opioid overdose was 1,862.8 per 100,000 person years, similar to rates reported in previous studies of ED patients with non-fatal opioid overdose.[15–17] The associated SMR (106.1) was also similar to

previous estimates.[14,17] Risk of unintentional overdose death was 30% higher among opioid overdose patients with comorbid diagnosis of sedative/hypnotic drug poisoning, underscoring the potential risks posed by combined use of opioids and sedative/hypnotics. [38,39,50]

Among sedative/hypnotic overdose patients without evidence of opioid involvement, risk of fatal overdose was 342.5 per 100,000 person years. Female sedative/hypnotic overdose patients had a higher hazard of unintentional overdose death than their male counterparts. To the authors' knowledge, no analogous estimates of unintentional overdose death among sedative/hypnotic overdose patients have been previously published. Although this rate was lower than that among opioid overdose patients, intervention efforts aimed at reducing sedative/hypnotic overdose patients' risk of unintentional overdose death are clearly warranted.[51] Such interventions could include medication,[15] community naloxone rescue,[52] patient education, and substance use treatment for patients with problematic use.[53]

Suicide mortality among opioid overdose patients was substantially higher than among sedative/hypnotic overdose patients. This pattern contrasts with findings from an older literature,[36,54,55] but is consistent with more recent results in a study of Veterans Administration patients with diagnosed substance use disorders,[35] although that sample differed considerably from ours in demographic and clinical composition. Research on the patient-level associations between opioid misuse and suicide risk remains scant,[19] and the current finding needs replication in other samples before concluding that opioid misuse has a particularly strong relationship with suicide risk. The authors could not, for example, account for potentially confounding of comorbid psychiatric and chronic pain conditions. Nevertheless, ED clinicians should be aware that following overdoses from especially opioids but also sedative/hypnotics, patients experience markedly elevated risk for future death by suicide. Widespread implementation of suicide risk screening in these patient groups holds potential as a suicide prevention measure.

Mortality from natural causes accounted for large majorities of deaths in the first year following opioid and sedative/hypnotic overdoses and occurred at very high rates (8,058 and 17,301 per 100,000 person years, respectively). The elevated risk of natural cause mortality faced by overdose patients is consistent with evidence that many opioid- and sedative-dependent patients have complex chronic health conditions and other risk factors that contribute to substantial compromise of their health status.[17,56] Effective ED-based interventions have been developed for drug overdose/misuse patients,[45,57] but focus primarily on preventing drug-related morbidity and mortality. Findings from this study suggest that new interventions are needed to more comprehensively address their mortality risks. Notably, though sedative/hypnotic overdose patients' absolute rate of natural cause death was higher than that of opioid overdose patients, this difference may be due in part to differences in the groups' demographic compositions.

Limitations

Per the study definition, the patient groups were mutually exclusive and assigned hierarchically; alternative analytic strategies exist but are unlikely to significantly alter the key findings. Diagnoses in ED contexts are prone to error and misclassification, and drug-

related diagnoses (e.g., comorbid sedative/hypnotic involvement) may be under-reported. Given this limitation, the substantial group differences in mortality are especially noteworthy. Additionally, although visits coded as deliberate self-harm were excluded, some of the index overdoses could have involved occult suicidal intent.[58] The administrative data set also lacked other clinical information that could be helpful for interpreting the results, such as patients' underlying medical illness burden, psychosocial circumstances, and history of filling prescriptions for or accessing illicit opioid and sedative/hypnotic drugs. Lastly, the study data are from California during 2009–2012, and therefore may not generalize to contemporary drug-related morbidity and mortality patterns and clinical practice throughout the country. For example, opioid-related mortality rates in California are lower than in other parts of the country, and after 2012 overdose deaths from heroin and fentanyl outnumbered those from prescription opioids, reflecting an evolving epidemic affecting different demographics. California also has nearly 38 million residents and 58 counties, potentially encompassing different practices for manner-of-death determinations. It was beyond the scope of this study to investigate or validate these determinations.

CONCLUSIONS

The high risk of fatal overdose, suicide, and other causes of death following emergency department visits for nonfatal opioid and sedative/hypnotic overdose highlights the need for intervention among these vulnerable patients, including immediate initiation of substance use disorder treatment[45] and integrated care models to comprehensively address mortality risk.[59] Although EDs play a key role in the acute medical stabilization of overdose patients, they can also serve as partners in longer-term harm-reduction strategies, including training caregivers in naloxone administration and initiating buprenorphine treatment when opioids are involved, as well as providing warm handoffs to mental health treatment and other outpatient care providers.[18,60] Although current emphasis has focused on ED patients presenting with opioid overdose, clinical attention should also be directed to patients presenting with sedative/hypnotic drug overdose, to help stem the tide of drug addiction and associated mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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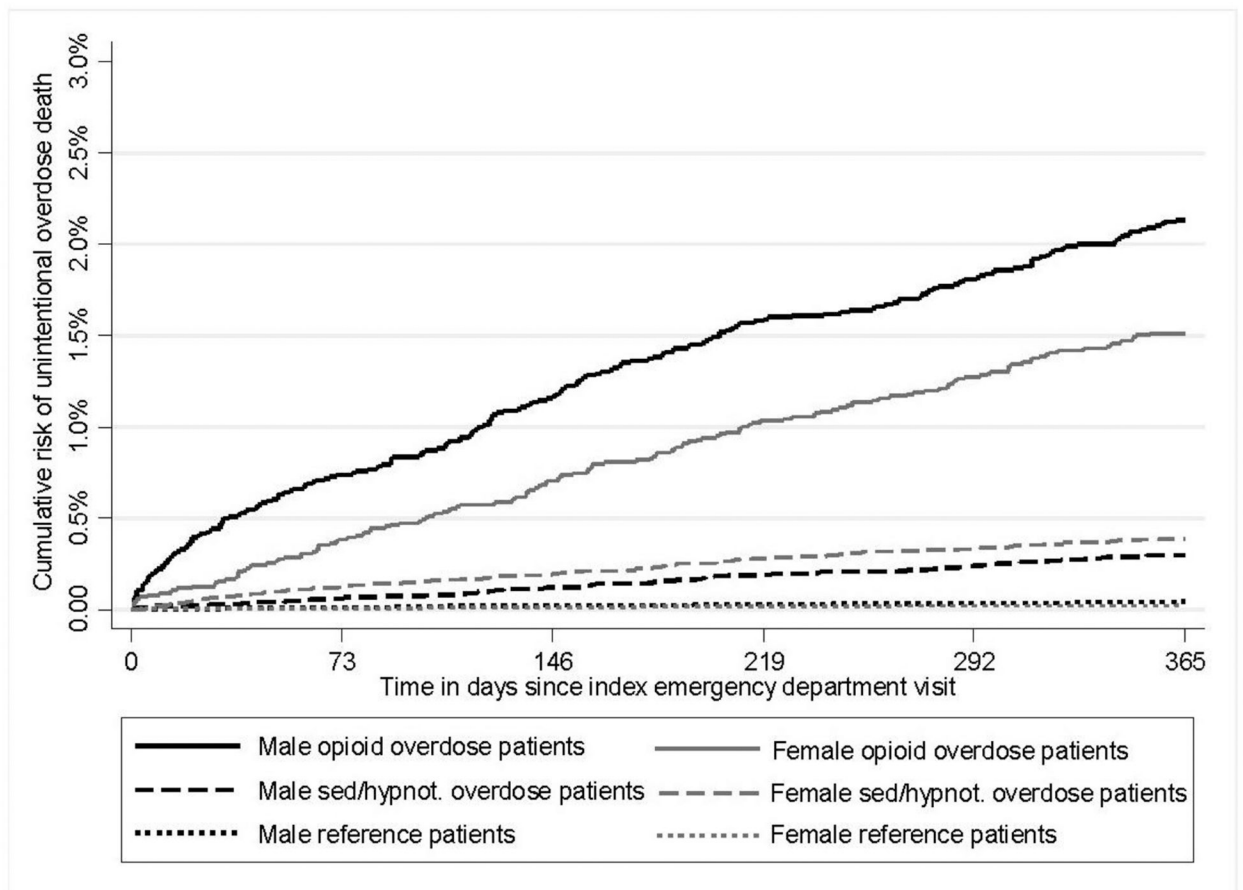**Figure 1.**
Kaplan-Meier cumulative probabilities of unintentional overdose death, by patient group and sex, for 365 days of follow-up during 2009–2012 among California emergency department patients. sed/hypnot., sedative/hypnotic.

Table 1.

Patient Characteristics Among 646,969 Patients Receiving Emergency Department Care for Opioid Overdose, Sedative/Hypnotic Drug Overdose, or Any Other Condition, California, 2009–2011

Patient characteristics at index visit	Drug overdose patients		Reference patients (n=500,216)
	Opioid overdose patients (n=21,080)	Sedative/hypnotic overdose patients (n=75,39T)	
Female sex, n (%)	10,362 (49.2)	35,473 (47.1)	270,846 (54.2)
Age, years, n (%)			
10–24	2,606 (12.4)	4,256 (5.7)	102,738 (20.5)
25–44	5,757 (27.3)	13,080 (17.4)	153,003 (30.6)
45–64	9,139 (43.4)	27,026 (35.9)	140,641 (28.1)
65	3,578 (17.0)	31,029 (41.2)	103,834 (20.8)
Race/ethnicity, n (%)			
Non-Hispanic white	14,517 (68.9)	42,397 (56.2)	247,911 (49.6)
Non-Hispanic black	1,886 (8.9)	8,352 (11.1)	47,225 (9.4)
Hispanic	3,524 (16.7)	16,637 (22.1)	136,723 (27.3)
Asian/Pacific Islander	341 (1.6)	5,254 (7.0)	37,485 (7.5)
Non-Hispanic other	812 (3.9)	2,751 (3.6)	30,872 (6.2)
Insurance type, n (%)			
Private	5,282 (25.1)	21,870 (29.0)	80,377 (16.1)
Medicare	5,908 (28.1)	34,337 (45.6)	79,459 (15.9)
Medicaid	5,168 (24.5)	12,912 (17.2)	85,592 (17.1)
Self-pay	4,181 (19.9)	4,887 (6.5)	234,919 (47.0)
Other	512 (2.4)	1,246 (1.7)	19,361 (3.4)

Table 2.

Unintentional Overdose, Suicide, and Other Mortality Within 1 Year Among California Emergency Department Patients Presenting in 2009–2011 With Opioid Overdose, Sedative/Hypnotic Drug Overdose, or Any Other Condition (Reference Patients)

Manner of death	Opioid overdose patients (N=21,080)			Sedative/hypnotic overdose patients (N=75,391)			Reference patients (N=500,216)		
	Deaths, n	Mortality per 100,000 p-y	SMR[a] (95% CI)	Deaths, n	Mortality per 100,000 p-y	SMR[a] (95% CI)	Deaths, n	Mortality per 100,000 p-y	SMR[a] (95% CI)
Unintentional injury									
Overdose	368	1,862.8	106.1 (95.2, 116.9)	232	342.5	24.5 (21.3, 27.6)	152	31.0	2.6 (2.2, 3.0)
Other causes	51	258.2	8.4 (6.1, 10.7)	156	230.3	5.1 (4.3, 5.9)	306	62.5	2.2 (2.0, 2.4)
All causes	419	2,120.9	44.0 (39.8, 48.2)	388	572.9	9.6 (8.7, 10.6)	458	93.5	2.3 (2.1, 2.5)
Suicide									
Overdose	29	146.8	43.0 (27.4, 58.7)	35	51.7	17.0 (11.4, 22.7)	32	6.5	2.8 (1.8, 3.8)
Other causes	34	172.1	12.3 (8.1, 16.4)	83	122.6	7.9 (6.2, 9.6)	125	25.5	2.3 (1.9, 2.8)
All causes	63	318.9	18.1 (13.6, 22.6)	118	174.2	9.2 (7.6, 10.9)	157	32.0	2.4 (2.0, 2.7)
Homicide	<11[b]	45.6	8.2 (2.9, 13.6)	<11[b]	11.8	11.6 (5.0, 18.2)	51	10.4	1.7 (1.2, 2.1)
Undetermined intent injury	15	75.9	47.3 (23.4, 71.3)	13	19.2	12.6 (5.8, 19.4)	13	2.7	2.1 (0.95, 3.2)
All external-cause injuries	506	2,561.3	35.1 (32.1, 38.2)	527	778.1	9.2 (8.4, 9.9)	679	138.6	2.3 (2.1, 2.4)
Natural causes	1,592	8,058.5	8.0 (7.6, 8.4)	11,718	17,301.5	8.6 (8.5, 8.8)	15,176	3,096.9	3.1 (3.1, 3.2)
All causes	2,098	10,619.9	9.9 (9.4, 10.3)	12,245	18,079.6	8.6 (8.5, 8.8)	15,855	3,235.5	3.1 (3.0, 3.1)

[a]Standardized Mortality Ratio: mortality by manner of ED group relative to mortality by manner of California population in 2009–2012 matched to the ED group by age, sex, and race/ethnicity. California data come from CDC WONDER detailed mortality tables (https://wonder.cdc.gov/ucd-icd10.html, accessed June 2019).

[b]Exact cell counts suppressed to protect patient confidentiality.

p-y, person-years.

Table 3.

Unintentional Overdose, Suicide, and Other Mortality Within 1 Year Among Subgroups of California Emergency Department Patients Presenting in 2009–2011 With Opioid Overdose

Manner of death	Opioid overdose patients with comorbid sedative/hypnotic diagnosis (N=4,186)		Opioid overdose patients without comorbid sedative/hypnotic diagnosis (N=16,894)		HR$_{adj}$ (95% CI)[b]
	Deaths, n	Mortality per 100,000 person-years	Deaths, n	Mortality per 100,000 person-years	
Unintentional injury					
Overdose	89	2,243.0	279	1,767.2	**1.30 (1.02, 1.66)**
Other causes	16	403.2	35	221.7	**1.83 (1.01, 3.32)**
All causes	105	2,646.3	314	1,988.9	**1.36 (1.09, 1.70)**
Suicide					
Overdose	<11[a]	252.0	19	120.4	1.94 (0.90, 4.20)
Other causes	<11[a]	201.6	26	164.7	1.28 (0.58, 2.84)
All causes	18	453.6	45	285.0	1.58 (0.91, 2.74)
Homicide	<11[a]	25.2	<11[a]	50.7	0.80 (0.10, 6.58)
Injury of undetermined intent	<11[a]	50.4	13	82.3	0.56 (0.13, 2.48)
All external	126	3,175.5	380	2,407.0	**1.34 (1.10, 1.65)**
Natural causes	241	6,073.8	1,351	8,557.4	**0.74 (0.65, 0.85)**
All-cause	367	9,249.3	1,731	10,964.3	**0.86 (0.77, 0.96)**

Note: Boldface indicates statistically significant association (*p*<0.05).

[a] Exact cell counts suppressed to protect patient confidentiality.

[b] Hazard ratios adjusted for patient age, sex, race/ethnicity, and payer at index visit.